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RE: National Coverage Analysis for Erythropoiesis Stimulating Agents (ESAs) for Non-Renal Disease Indications (CAG-00383N)

Dear Dr. Phurrough:

The American Society of Hematology (ASH) represents over 11,000 hematologists in the United States who are committed to the treatment of blood and blood-related diseases. ASH members include hematologists and hematologist/oncologists who regularly render services to Medicare beneficiaries. The Society appreciates this opportunity to comment on the Proposed Decision Memo for Erythropoiesis Stimulating Agents (ESAs) for non-renal disease indications (CAG-00383N).

Of paramount importance to ASH is to ensure that all coverage decisions are guided by the best available scientific evidence to ensure the highest degree of patient safety and to protect against not only the overuse of ESAs, but their underuse and misuse as well. Consequently, the Society is deeply concerned that CMS's proposed decision memo inappropriately restricts use of ESAs because a number of its proposals are not supported by scientific data, rely on poor quality data, or are in conflict with expert scientific analysis.

In addition, ASH is concerned that CMS's proposed decision memo does not take into consideration the discussion during FDA's May 10, 2007 Oncology Drug Advisory Committee meeting, particularly a conclusion that the anemia of myelodysplasia (MDS) should not be included in decisions for restricted use. As FDA is the agency responsible for evaluating drugs for safety and efficacy, ASH believes CMS should not issue its proposal prior to the FDA's scientific review and final decisions on this issue.

Further, ASH notes that the proposed CMS restriction on MDS conflicts with a CMS-approved quality measure for the Physician Quality Reporting Initiative (PQRI). The quality measure involves the use of ESAs in MDS patients (see http://www.cms.hhs.gov/PQRI/Downloads/PQRIMeasuresList.pdf).

68. Myelodysplastic Syndrome(MDS): Documentation of Iron Stores in Patients Receiving Erythropoietin Therapy: Percentage of patients aged 18 years and older with a diagnosis of MDS who are receiving erythropoietin therapy with documentation of iron stores prior to initiating erythropoietin therapy.

ASH developed this evidence-based quality measure with consultation by CMS because of the recognized value of using ESAs to treat these patients. The measure was vetted through the Society and the AMA Physician Consortium for Performance Improvement, endorsed by the AQA, and then approved by CMS as part of the PQRI program. The proposal to restrict coverage in patients with MDS is contrary to the PQRI where CMS recognizes MDS as a condition for which ESA treatment can be considered a standard of practice. Consequently, CMS's proposed restriction for MDS contradicts the national consensus about appropriate quality care and demonstrates a lack of internal consistency within the agency.

ASH's comments on the proposed NCD follow. We note that because all ESAs have the same mechanism of action, ASH believes that the NCD should apply to all ESAs (marketed as Procrit, Epogen, and Aranesp). While some local carriers have separate coverage policies for darbepoetin alfa (Aranesp) and epoetin alfa (Epogen and Procrit), ASH believes there should be a single national coverage policy because the products are basically interchangeable and use of one is essentially equal to the use of the other.

Coverage of ESAs for Patients with Conditions Other than End-Stage Renal Disease

Anemia of Myelodysplasia -

In its proposed decision memo, CMS proposes broad coverage restrictions to the FDA-approved indication for ESAs in chemotherapy-induced anemia and broad restrictions for off-label uses. ASH strongly disagrees with CMS's conclusion that there is sufficient evidence to restrict coverage of ESAs for treatment of the anemia of myelodysplasia (MDS). To the contrary, there is evidence to support the use of ESAs in patients with anemia associated with MDS with less than five percent blasts.

Definition of Myelodysplasia: Myelodysplastic syndromes (MDS) are a heterogeneous group of hematological malignancies characterized by dysplastic and ineffective hematopoiesis and a variable risk of transformation to acute leukemia. MDS with less than five percent blasts can include the following (World Health Organization classification) forms of MDS:

- Refractory anemia (RA) (238.72)
- Refractory anemia with ringed sideroblasts (RARS) (238.72)
- Refractory cytopenia with multilineage dysplasia (RCMD) (238.72)
- Refractory cytopenia with multilineage dysplasia and ringed sideroblasts (RCMD-RS) (238.72)
- Myelodysplastic syndrome, unclassified (MDS-U) (238.75)
- MDS associated with isolated del(5q) (238.74)

Refractory anemia can be defined as a red cell production deficiency that cannot be assigned to a specific vitamin or mineral deficiency.

ASH recommends that Medicare cover treatment with ESAs in patients with MDS who meet the following criteria:

1. Hemoglobin (Hgb) of 10 g/dl or Hematocrit (Hct) of 30% or less
2. Patients who have a reasonable expectancy of longer survival
3. Patients who need or are anticipated to need frequent transfusions
4. Treatment with ESAs will end or reduce the need for transfusions

Scientific Rationale for Coverage: Since the FDA approved epoetin as a pharmaceutical in 1989 for anemia of chronic renal failure, numerous studies have examined its potential use as an alternative to transfusions in the management of anemia in patients with cancer and specifically in patients with MDS. CMS should consider this evidence.

Published data on the safe and effective use of ESAs in MDS patients spanning more than a decade are available. Examples include: A randomized double-blind placebo-controlled study with subcutaneous recombinant human erythropoietin in patients with low-risk myelodysplastic syndromes (Italian Cooperative Group,1998) and Treatment of anemia in myelodysplastic syndromes with granulocyte colony-stimulating factor plus erythropoietin: results from a randomized phase II study and long-term follow-up of 71 patients. (Hellstrom-Lindberg et al, 1998). Studies with long-term follow-up have shown no negative impact on survival or evolution to leukemia (Jadersten M et al, 2005). In fact, these studies have shown that ESAs with or without G-CSF (granulocyte colony stimulating factor) can induce long-lasting responses and transfusion independency in defined subsets of MDS patients. A recent pooled analysis of nearly 2600 individuals with low-risk MDS indicated that those receiving ESAs with or without G-CSF demonstrated greater overall and progression-free survival than those patients who did not receive growth factors, after controlling for baseline patient characteristics. (Golshayan AR et al, 2007).

Even more recent studies, some in abstract form but with manuscripts in preparation, continue to buttress the role of ESAs for patients with MDS without evidence that ESAs increase the rate of transformation to acute leukemia. Miller, et al., reported on 105 MDS patients treated with either supportive care or erythropoietin (EPO). (Miller KB, et al 2004, manuscript in preparation). In this study, the response rate, defined as at least a decrease in transfusion requirement, was 35% in the EPO (erythropoietin) arm and 9% in the supportive care arm ($p=.002$). Transformation to AML (acute myeloid leukemia) occurred in 3.6% of patients on supportive care and 0.0% of patients receiving EPO. Toxicities were comparable across all patients. Neither EPO nor the addition of G-CSF was associated with an increased rate of transformation to acute leukemia. In another trial the effect of growth factor treatment was evaluated in 363 patients with MDS with different probability of response. All patients were transfusion dependent (n=176) or anemic with hemoglobin level below 10 g/dL (n=187). The erythroid response (transfusion independence) was seen in 41% of treated patients with median duration of 23 months (range: 3-116+). There was no significant impact on risk of leukemic transformation in patients with low ($p=0.75$) or high ($p=0.21$) transfusion need. (Jadersten M, et al 2006.).

This is a sampling of studies addressing the long term use of erythropoietin with or without G-CSF in MDS patients compared to either randomized controls or historical controls. These studies have shown no negative impact on survival or leukemic evolution and, thus, these data conflict with and do not substantiate CMS's statement that the evidence is sufficient to conclude that ESA treatment is not reasonable and necessary for these Medicare beneficiaries because of a possible deleterious effect of the ESA on their underlying disease. Indeed, they provide strong evidence that treatment of anemia in MDS patients with erythropoietin with or without G-CSF can induce positive effects, including long-lasting transfusion independence without risk of leukemic transformation.

To ensure that CMS's final decision memo for ESAs reflects the state of the science and is based on principles of evidence-based medicine, CMS needs to consider these data on the safe and effective use of ESAs in MDS patients. (See also Hellstrom-Lindberg, 2005, Hellstrom-Lindberg, Eva, et al.,.2003; Terpos, Evangelos, et al.,. 2002; Hellstrom-Lindberg, Eva, et al.,1998;; Hellstrom-Lindberg, Eva, et al, 1997; Stein, Richard S., et al,1991).

It is also important to note, that the studies showing significant and life-threatening events in certain patients who were treated with ESAs for non-renal diseases do not appear to have included patients with MDS, but only patients who had end-stage solid cancers and/or renal disease. In addition, in those studies, the patients' hemoglobin levels typically were kept above 12 g/dl while patients with MDS and other bone marrow failure syndromes s rarely reach a hemoglobin level that high. Thus, findings from these studies should not be applied to patients with MDS.

ASH understands that CMS is concerned about potential risks that can be associated with use of ESAs (cardiovascular, thrombotic events, hypertension) documented in physician references, such as Micromedex. While ASH supports use of these types of references and guidelines to help physician decision making, the Society also recognizes that specialists who treat complex hematologic diseases must also consider each patient's individual circumstance and the standard of practice in the community to determine appropriate care. Removing coverage for ESAs for patients with MDS will be an arbitrary policy that is not justified by sufficient scientific evidence, does not reflect the standard of practice of experts in the field, and that will harm some Medicare beneficiaries.

Other Proposed Restricted Conditions -

ASH proposes clarification on the following conditions for which CMS is seeking public comment that "ESA treatment is not reasonable and necessary for beneficiaries either because of a deleterious effect of the ESA on their underlying condition or because the underlying disease increases their risk of adverse effects related to ESA use":

- The anemia of myeloid cancers: As discussed above, MDS should be excluded from this restriction.

- The anemia of cancer not related to cancer treatment: Erythroid hypoplasia leading to anemia may occur weeks to months following cessation of chemotherapy or radiation therapy. This may be the first sign of MDS, however MDS may never develop. The use of ESAs may decrease transfusion requirements in these patients. Even though the causal relationship between the anemia and previous treatment may be difficult to document, it would be reasonable not to exclude these patients from receiving ESAs.
- Any anemia associated with radiotherapy: Many patients receive chemotherapy concomitant with radiotherapy, or in series with radiotherapy. The restrictive language should be specific for anemia during primary treatment with radiotherapy.
- Patients with thrombotic episodes related to malignancy: There is no clinical evidence that these patients are at higher risk for complications related to treatment with ESAs. There is, of course, much published evidence demonstrating that an increase incidence of thrombotic episodes are related to certain malignancies and with certain therapies in the treatment of malignancies. Appropriate anticoagulation may be required. Given the concern of a general increase in VTE when ESAs are used to increase the hemoglobin above 12 g/dl, physicians need to carefully monitor the hemoglobin in these patients, as they would for any patient receiving ESAs.

CMS Proposed NCD Treatment Limitations

1. *The hemoglobin/hematocrit levels immediately prior to initiation of dosing for the month should be<9 g/dl/27% in patients without known cardiovascular disease and <10 g/dl/30% in patients with documented symptomatic ischemic disease that cannot be treated with blood transfusion-*

ASH opposes CMS's proposed policy of initiating therapy at 9 g/dl in each month because it is not supported by scientific evidence. CMS has not provided any clinical or scientific rationale for setting a hemoglobin upper limit at 9 g/dl when the recently revised FDA label is not to exceed 12 g/dl. ESAs should be started in appropriate clinical settings at a hemoglobin level at or below 10 g/dl/ 30%. It should be understood that the hemoglobin level of 10 g/dl is not a trigger, but guidepost for the assessment of the patient's physiologic needs. ASH notes, however, that there may be extenuating circumstances when treating patients with co-morbidities, such as cardiac or pulmonary disease, (which should be documented) that could justify use of ESAs before the hemoglobin has decreased to 10 g/dl/30%.

The therapeutic goal should be a hemoglobin level of no higher than 12 g/dl and recommends that the dose of ESA be modified in accordance with the recent FDA black box warning when the hemoglobin approaches 12 g/dl. ASH believes it is important to encourage doctors to be vigilant in monitoring patient blood counts when treating with ESAs and iron levels in non-responders.

2. Maximum Covered Treatment Duration

ASH believes that the treatment recommendation should be based upon the disease and CMS's proposed limitation of 12 weeks is without support in the clinical evidence and should be re-evaluated. Chemotherapy regimens are frequently prolonged and may last beyond 12 weeks. In

addition, patients experience a variable number of courses of chemotherapy in a year depending on tumor type, extent of disease, and response to therapy. As such, CMS's proposal is arbitrary and could hurt Medicare beneficiaries who are prescribed chemotherapy regimens in excess of 12 weeks or who require multiple courses in a year.

Further, ASH notes that a patient may continue to suffer from anemia for some time following completion of chemotherapy treatment and consequently recommends that coverage of ESAs be continued for treatment of anemia for 90 days post chemotherapy. If the anemia persists beyond 90 days after completion of chemotherapy, it would be reasonable to re-evaluate the anemia to determine if this continues to be a result of the chemotherapy, thereby justifying continuation of ESA treatment, or if another process is in place. ASH believes most patients should recover within this time period, but notes evidence from randomized clinical trials concerning this issue is not available and recommends prospective studies concerning this topic.

3. Maximum Covered Treatment Dose

CMS's proposed restriction is inconsistent with the FDA-approved dosing regimen for ESAs. The dose of ESAs is to be titrated drugs used to achieve specific hemoglobin levels. The starting doses and dose adjustment guidelines are clearly delineated in the product label and clinical practice guidelines. Moreover, the FDA-approved labeling for darbepoetin alfa states that one of the product's dosing regimens allows for administration at a dose of 500 mcg every three weeks (*i.e.*, up to 1,000 mcg per six weeks unless there are dose reductions). Limiting the total dose of darbepoetin alfa to 630 mcg per 4 weeks will limit the ability for physicians to effectively manage anemia in patients who may require a higher than average dose to respond and disadvantage patients who are prescribed every-three-week dosing given with their chemotherapy regimens. Similarly, the labeled dose of epoetin alfa is 40,000 U per week and the product label recommends an increase to 60,000 U per week (*i.e.*, 360,000 U per six weeks), for patients who do not have satisfactory response after 4 weeks of therapy. (Rizzo DJ, Lichtin AE, Woolf SH, et al, 2002)

4. Discontinue Use of ESA in Non-Responders After 4 Weeks

ASH believes CMS's proposal is not based on scientific evidence. ESAs should not be continued after six to eight weeks in the absence of response, assuming the appropriate dose increase (titration) has been attempted in low-responders.

5. Discontinue Use of ESA if Increase in Fluid Retention

ASH believes this proposal is not founded in scientific evidence. Because this recommendation is not based on clinical evidence, it should be removed from the final decision memo.

6. Discontinue Use of ESA if Rapid Rise in Hemoglobin/Hematocrit

While ASH agrees that patients should not experience too rapid a rise in their hemoglobin/hematocrit level, the proper response, as with other medical interventions, should be for the physician to make a dosage adjustment not to discontinue use. ASH believes this proposal should be removed from the final decision memo.

CMS Proposal to Allow ESA Therapy for Beneficiaries with Cancer Only Within Clinical Research Studies

ASH opposes CMS's proposal that ESAs be available to Medicare beneficiaries only in the context of clinical studies. This proposed restriction for an FDA-approved indication would be inappropriate and unprecedented for any Medicare covered drug or biological. Further the proposal is not justified based on the multitude of published evidence supporting ESA use. Therefore, this proposal should not be finalized.

Additional Concerns with CMS Proposed NCD

Impact of Transfusions as Alternative Treatment -
The alternative to ESA therapy would be transfusion. In patients with MDS, where chronic transfusions would substitute for the use of ESAs, the risks would be substantial and would include alloimmunization, TRALI (transfusion-related lung injury), and iron overload. The treatment of iron overload in and of itself carries substantial risk to the patient. Furthermore, the inconvenience to the patient and the impact on the quality of life associated with transfusions should be taken into account in these chronically ill patients.

ASH also notes that ESAs help to reduce the need for transfusions and thereby alleviate strain on the nation's blood supply. Therefore, the impact on the blood supply also should be taken into account when determining changes in the use of these products.

Additional Research Needed –

ASH acknowledges that we need to learn more about the optimal uses and potential side-effects of ESAs. The use of ESAs in the area of hematologic malignancies requires further clinical study. ASH encourages the development of larger Phase III studies, perhaps under the CMS CED program to help answer these questions.

Conclusion

In conclusion, ASH has deep concerns about the proposed NCD. Based on scientific evidence and expert consensus of clinicians, the Society opposes the proposed restriction for anemia of MDS and the proposed limitations on ESA treatment dose and duration. While emerging safety concerns raised in recent studies indicate the need for CMS to review its policies concerning ESAs, ASH believes the proposed NCD inappropriately restricts use of ESAs because a number of the proposals are not supported by the preponderance of scientific data or are in conflict with expert scientific analysis.

ASH would like to work with CMS as the agency evaluates the evidence for its proposed coverage policy and the consequences of the proposal on patients with MDS and other

hematologic malignancies. ASH is currently finalizing revisions to its evidence-based clinical practice guidelines on ESAs with the American Society of Clinical Oncology. The updated guidelines are expected to be published in September and we will share them with CMS upon their completion. In the meantime, please do not hesitate to contact the Society at mbecker@hematology.org if we can answer any question or provide assistance.

Sincerely,

Andrew I. Schafer, MD
President

Samuel Silver, MD, PhD
Chair, ASH Reimbursement Subcommittee
Councilor, ASH Executive Committee

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